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Hypothalamic Food Intake Regulating Areas are Involved in the Homeostasis of Blood Glucose and Plasma FFA Levels

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STEFFENS, A. B., A. J. W. SCHEURINK, P. G. M. LUITEN AND B. BOHUS. *Hypothalamic food intake regulating areas are involved in the homeostasis of blood glucose and plasma FFA levels.* *PHYSIOL BEHAV* 44(4/5) 581-589, 1988.—The hypothalamus fulfills multiple functions, e.g., integration of food and water ingestion, various forms of social behavior and physiological neuroendocrine activities. Hypothalamic areas, particularly the ventromedial, lateral and paraventricular areas (VMH, LHA and PVN respectively), that contribute to the regulation of food intake are also involved in the regulation of blood glucose and plasma free fatty acid (FFA) levels. This regulation is controlled both directly via neural pathways and indirectly by hormones, e.g., insulin, glucagon, norepinephrine (NE) and epinephrine (E). A description is presented of the intrahypothalamic connections and the pathways between the hypothalamus and the motor areas of both the sympathetic system in the spinal cord (the intermediolateral column IML) and the parasympathetic system in the brainstem (the dorsal motornucleus of the vagus and the nucleus ambiguus). Noradrenergic stimulation of the LHA, VMH and PVN can alter blood glucose, plasma FFA and insulin levels independently of each other, e.g., noradrenergic stimulation of the VMH leads to an increase of insulin, glucose and FFA. Exercise induced increases of glucose are suppressed by α -adrenergic blockade of the LHA, VMH and PVN. Alpha-adrenergic blockade of the VMH during exercise causes an exaggerated increase of plasma FFA whereas α -blockade of both the LHA and PVN does not change the normal exercise induced increase of plasma FFA. The apparent contradiction that both adrenergic stimulation and adrenergic blockade of the VMH result in an increase in FFA may be explained by assuming postsynaptic α - and β -adrenergic receptors in the VMH controlling glucose and FFA release respectively and FFA release and presynaptic inhibitory α -adrenergic receptors. Many of these changes are mediated through the circulating catecholamines NE and E. This humoral mechanism may also contribute to the regulation of complex cardiovascular changes that occur in relation to sympathetic activation during energy expenditure such as exercise.

Ventromedial hypothalamus	Lateral hypothalamus	Paraventricular nucleus	Blood glucose
Plasma FFA	Plasma insulin	Plasma catecholamines	Blood pressure
Autonomic nervous system			Heart rate

SINCE the original observations by Hetherington and Ranson in 1940 (18) that lesioning of the ventromedial hypothalamic area (VMH) causes hyperphagia and obesity, much evidence has accumulated that the VMH has a wider function than only the regulation of food intake. Among others, the VMH also participates in the regulation of sexual and aggressive behavior (23,39). In addition, many other hypothalamic and adjacent structures play a role in food intake and body weight regulation. Lesioning of the dorsomedial nucleus of the hypothalamus (DMH) results in a diminished food intake and body weight (5,6). Destruction of the lateral hypothalamic area (LHA) leads to temporary aphagia and permanent reduction of body weight (1,21). Knife cuts parasagittally of the VMH probably damaging neural pathways between the LHA and paraventricular nucleus (PVN)

elicit hyperphagia and obesity (41). Therefore the PVN might be considered as a part of the satiety mediating system. Accurate analysis of the function of the PVN has demonstrated that the role of the PVN in this respect might be even more important than that of the VMH (3).

The above mentioned hypothalamic structures are not functioning as independent regulators but are parts of extended neuronal networks with many interconnections and branches of descending neurons (see following paragraphs). In addition, the functioning of this network depends on the activity of ascending pathways such as the ventral and dorsal noradrenergic bundles running from several loci in the brainstem to the forebrain. Both bundles project on several hypothalamic areas on passing the hypothalamus.

The hypothalamus not only affects behavior but also

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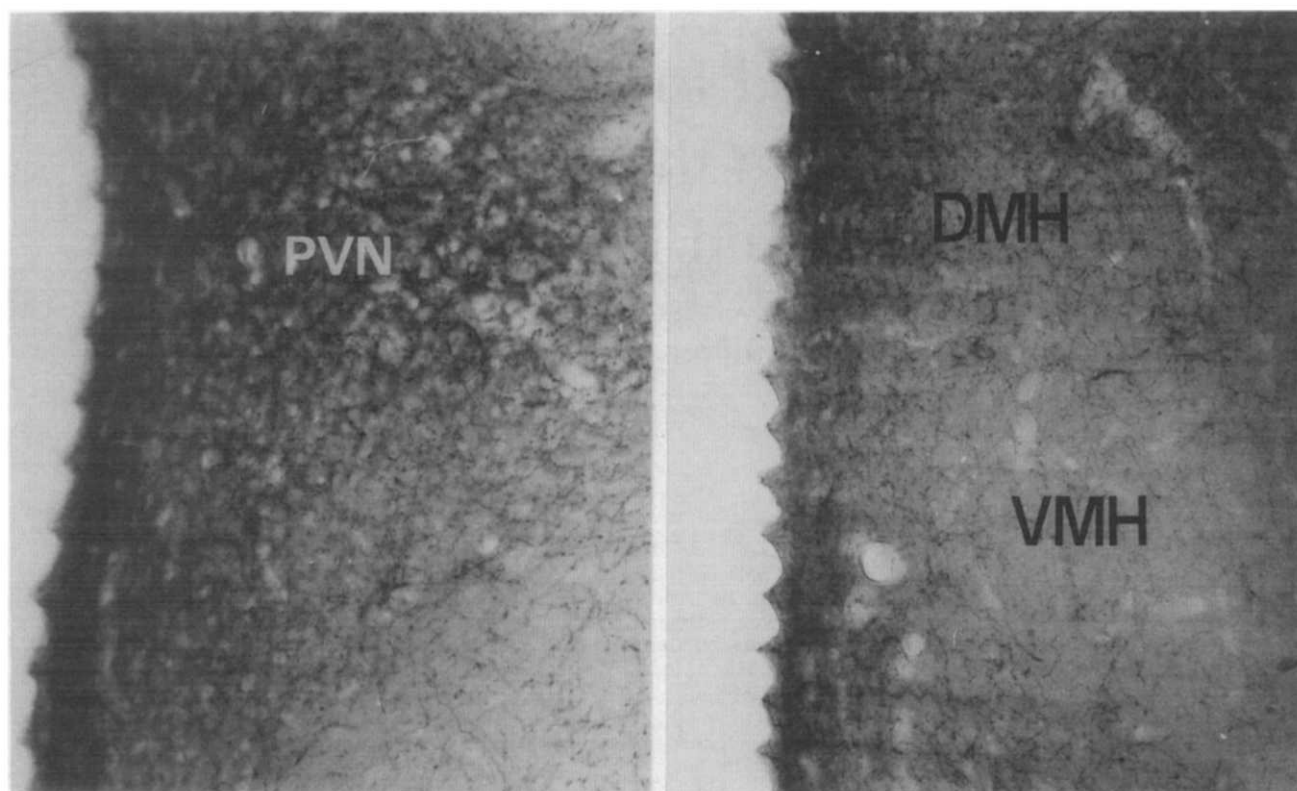


FIG. 1. Photomicrographs of immunoreactivity to norepinephrine in the PVN region (left panel) and in the DMH/VMH area (right panel). A relatively dense pattern of immunoprecipitate is present in the PVN which can be recognized by its characteristic triangular shape. The DMH is provided with a medium density supply of noradrenergic input, whereas the VMH is basically free of such fibers. Photographs taken from vibratome sections treated with primary antiserum against norepinephrine followed by the PAP sandwich immunocytochemical procedure.

many neuroendocrine functions via both the pituitary and the autonomic nervous system. By means of these mechanisms the hypothalamus is involved in the regulation of plasma glucose and free fatty acid (FFA) levels, the main substrates to cover energy expenditure in the body (43,49). Until now relatively little attention has been paid to this function of the hypothalamus. Its involvement is probably the most important during increased demand of glucose and FFA. Such a condition is, for example, physical activity, particularly exercise. The regulation of energy expenditure cannot be separated from the blood supply—i.e., the regulation of heart rate and blood pressure (9,47). Many investigations suggest that hypothalamic areas that control glucose and/or FFA levels also participate in the regulation of heart rate and blood pressure. This short review aims to summarize the neural interconnections between hypothalamic areas and the neural connections between the hypothalamus and the motor pools of the preganglionic neurons of the autonomic nervous system. Furthermore, data are presented on the involvement of the hypothalamus in the homeostasis of blood glucose and plasma FFA levels during rest and exercise as well as on heart rate and blood pressure changes during exercise in the rat.

INTERCONNECTIONS BETWEEN HYPOTHALAMIC AREAS AND CONNECTIONS BETWEEN THE HYPOTHALAMUS AND THE AUTONOMIC NERVOUS SYSTEM

Neuroanatomical studies related to hypothalamic

cell groups that are possibly involved in feeding and related homeostatic control functions have traditionally been focussed on the ventromedial and lateral hypothalamic nuclei (1, 43, 47). Both regions have been long considered as antagonist counterparts in a rather simplistic view on "dual center" hypothesis of substrate regulation (37). This view is abandoned since ample evidence is available now that various intra- and extrahypothalamic regions exert profound effects on regulation of body weight and limbic functions in general (6, 26, 28, 32). For example, more recent experimental data clearly indicate that a major role in limbic regulation of the hypothalamus must be attributed to the paraventricular hypothalamic nucleus (PVN). Hence, it seems to be more accurate to consider hypothalamic nuclei as crucial links in an output chain from 'higher' integrative limbic centers, as amygdala and limbic cortex, to the neuroendocrine and autonomic nervous system. However, apart from its function in limbic output, the hypothalamus is also a level of integration in itself, receiving a considerable direct vegetative input from primary sensory nuclei of the lower brainstem (17,38).

When studying the sources of input to the various hypothalamic nuclei, it is a remarkable finding that only limited input from higher limbic regions have direct access to the PVN. In this respect, the VMH, DMH and especially the LHA are recipients of a considerable input from the limbic cortex (mainly to LHA), amygdala (to VMH and DMH) and from structures like the septum and bed nucleus of the stria terminalis (32). Direct limbic input to the PVN appears to be

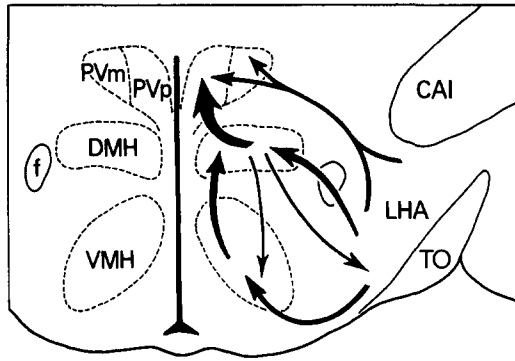


FIG. 2. Diagrammatic survey of the major connections between VMH, DMH, PVN and LHA. The thickness of the arrows is indicative for the relative density of the various projections. Note a predominant flow of connectivity to the parvocellular PVN.

limited to some afferents from prefrontal cortex and bed nucleus as may be concluded from a variety of anterograde and retrograde intraaxonal transport studies (30,40). The PVN is the recipient of strikingly strong inputs from structures conveying information more directly from the peripheral, physiological state of the organism. The PVN receives input from various circumventricular organs as subfornical organ, organum vasculosum, lamina terminalis and probably also from the area postrema (40,51). An important source of input to the hypothalamus in general and to the PVN in particular is indicated by immunocytochemical staining of fibers on their reactivity to norepinephrine (NE). The importance of NE innervation of the various hypothalamic nuclei under study, is further emphasized by the powerful effects on feeding and body weight by chemical stimulation with NE (24-26). In the search of the source of the NE innervation of the hypothalamus we have compared NE immunocytochemistry with anterograde tracing of pathways from the posterior solitary tract nuclei to the hypothalamus employing the intraaxonal transport of Phaseolus vulgaris leucoagglutinin (15,54). From these data we may conclude that noradrenergic neurons in the nucleus of the solitary tract (NTS) and dorsal motor vagus nucleus (cell group A2) are the major source of noradrenergic innervation of the hypothalamus via the ventral noradrenergic pathway. A second but probably largest noradrenergic lower brainstem projection to the parvocellular division has been described to originate from the A1 cell group, whereas a third and less extensive NE input comes from the Ab region of the locus coeruleus (51). This pattern of noradrenergic NTS input to the hypothalamus is very dense in the PVN, fairly well-developed in DMH, LHA and periventricular region, but virtually absent in the VMH (Fig. 1). With regard to the functional character of this input it may be emphasized that the NTS is the recipient of chemical sensory input from the alimentary tract and related organs, carried mainly by the sensory branches of the facial, glossopharyngeal and vagal nerves (17). In addition, the NTS is the site of the first synapse of the baroreceptor input from the circulatory system (38).

From studies on the connectivity between PVN, VMH, DMH and LHA within the hypothalamus it may be concluded that the pattern of fiber relations indicates streams of information from VMH and LHA via the DMH to the PVN (Fig. 2). From a large number of anterograde tracing experiments, the DMH emerges as a major site of origin of short,

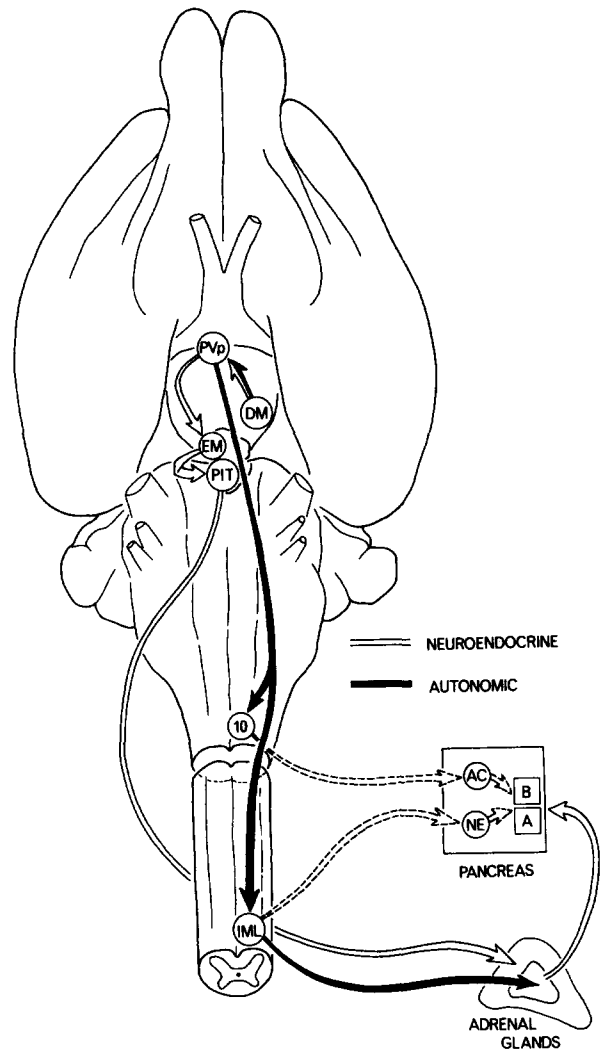


FIG. 3. Summary of neuroendocrine (open arrows) and autonomic (solid black arrows) pathways originating from the PVN. The neuroendocrine pathway consists of PVN projections to the median eminence (EM) and a subsequent vascular outflow to the pituitary (PIT). The autonomic pathway is made up of direct neural connections from PVN to parasympathetic (10) and sympathetic (IML) cell groups to brainstem and spinal cord. Each have connections to cholinergic (AC) and noradrenergic (NE) cell groups in the visceral organs (here represented by the pancreas with its A and B-cells). Arrows to the pancreas are interrupted for lay-out reasons only.

but very dense projections to the parvocellular position of the PVN. Some direct projections are also present from LHA to the PVN, but the general circuitry is characterized by rather dense pathways from both VMH and LHA to the DMH. As such the DMH takes the portion of an intermediary structure between various intrahypothalamic inputs on their way to the PVN (53,55). The DMH, however, is not only a mediator of information within the hypothalamus, but also has a clear function in its own which is demonstrated by a characteristic pattern of output pathways to a variety of brain regions such as the circumventricular organs (53,56). Intrahypothalamic connections between VMH and LHA, although present, are not very extensive and probably do not play a very crucial role in tuning the antagonistic activities of

their neurons. It is likely that the known opposite effects in feeding which result from VMH and LHA damage result from a differential pattern of, e.g., autonomic output of VMH and LHA.

Tracing studies on output connections of PVN, VMH, DMH and LHA revealed that each of these nuclei has its own channel of output to the neuroendocrine and/or autonomic nervous system. The PVN, in terms of output connectivity, is the most outstanding nucleus of the hypothalamus (Fig. 3). Parvocellular and magnocellular subdivisions of the PVN each maintain a variety of direct and indirect neuroendocrine pathways to anterior and posterior lobes, respectively, of the pituitary. The major indirect pathway consists of parvocellular projections to the median eminence where releasing factors (e.g., corticotropin releasing factor, CRF) reach the vascular blood supply of the pituitary. Here, CRF induces the secretion of adrenocorticotrophic hormone (ACTH) which regulates release of corticosteroids from the adrenal cortical tissue. Apart from the PVN, we also revealed a direct projection from the DMH to the posterior lobe of the pituitary. Since the DMH also contains a population of vasopressinergic neurons (11), the DMH connection to the pituitary may well be a vasopressin pathway. Apart from CRF also vasopressin can elicit ACTH release from the pituitary. CRF causes ACTH release from ACTH releasing pituitary cells by activation of adenylcyclase whereas vasopressin induces ACTH release through separate receptors by activation of phosphodiesterase resulting in hydrolysis of phosphatidyl inositol 4.5 diphosphate (PIP_2) (2).

A second characteristic of the PVN is its circumscribed direct connection to both sympathetic and parasympathetic preganglionic nuclei in brainstem and spinal cord. Without synaptic relay PVN neurons make direct contacts with the parasympathetic cell groups in nucleus ambiguus and motor vagus nucleus (31). A second pathway from PVN fibers travels through the lateral funiculus and forms a direct innervation of the entire sympathetic cell column in the intermediolateral region (IML) of the thoraco-lumbar segments of the spinal cord (31). Ambiguus and motor vagus nucleus, and IML were shown to house the preganglionics of parasympathetic and sympathetic innervation, respectively, of the majority of the visceral organs (32).

Although the PVN should be considered as the most direct link of the hypothalamus to the autonomic nervous system, DMH, VMH and LHA each have their own efferent channels to autonomic targets via brainstem and spinal cord (Fig. 4). The VMH has a very dense projection to the periaqueductal gray (PAG) from where a secondary projection originates to ventromedial and ventrolateral aspects of the lower medullary reticular formation (32). The ventromedial medulla on its turn has an extensive output to the entire IML and should be considered as a general sympathetic autonomic connection. The ventrolateral medullary region has preponderant projections to the motor pool of the cervical cord and is probably related to cardiovascular control functions. The LHA output pathways partly share the PAG connections described above for the VMH, but moreover has a direct projection to the parasympathetic cell groups in the lower brainstem. The DMH-autonomic connection is not very extensive. There are some DMH-PAG connections and a few direct efferent projections to the parasympathetic dorsal motor vagus neurons (53). It appears, however, that the DMH exerts its strongest autonomic influence via its impressive projection to the PVN (53).

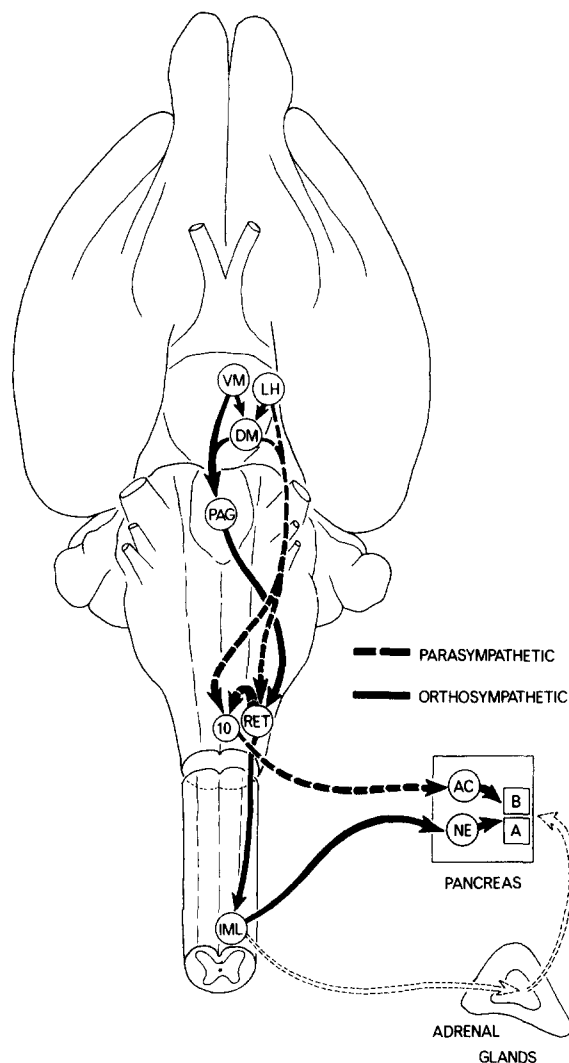


FIG. 4. Survey of autonomic pathways from lateral hypothalamus (LH), ventromedial (VM) and dorsomedial hypothalamic nuclei (DM). The majority of parasympathetic LH connections are aimed at the dorsal motor vagus nucleus directly, or indirectly via the lower medulla reticular formation (RET). The more sympathetic pathways from the VM (and partly DM) run via the periaqueductal gray (PAG) to various cell groups in the RET. From there, connections originate linking the lower medulla to sympathetic cell groups in the IML.

HYPOTHALAMIC EFFECTS ON THE HOMEOSTASIS OF BLOOD GLUCOSE AND PLASMA FFA

The first indication for a possible involvement of the autonomic nervous system in peripheral nutrient levels emerged from the work of Kaneto *et al.* (20) who demonstrated an increase of insulin release after electrical stimulation of parasympathetic vagal nerves to the pancreas. Electrical stimulation of the sympathetic splanchnic branches to the pancreas elicited glucagon release (7). Shimazu (42) reported that electrical stimulation of the vagal nerves to the liver resulted in increased glycogenesis, whereas electrical stimulation of splanchnic nerves to the liver led to glycogenolysis. These effects occurred by direct actions of the autonomic nervous system on the liver and were independent of insulin

and glucagon. Accordingly, stimulation of peripheral parts of the autonomic nervous system affects glucose release both directly by interfering with glycogenesis and glycogenolysis in the liver and indirectly by interfering with hormone release from the islets of Langerhans and the adrenals. Since free fatty acids (FFA) are another major fuel for most cells of the body the question can be raised whether or not lipogenesis and lipolysis are dependent of similar mechanisms. This is intriguing because in contrast to brown adipose tissue cells the white fat cells, the suppliers of FFA, do not receive direct autonomic innervation (43).

Much evidence is now available that the hypothalamus may affect metabolic control. In the previous paragraphs a description was presented of the connections of several hypothalamic areas with the motor pools of the preganglionic nerves of the autonomic nervous system. This network represents the anatomical hardware of the nervous control of metabolism. Lesioning of the VMH resulted in an immediate increase in activity in pancreatic vagal nerves and decrease in splanchnic nerve activity at the onset of the lesion whereas lesioning of the LHA led to exactly the reverse pattern (58). Electrical stimulation of the VMH led to an increased conversion of inactive phosphorylase b to active phosphorylase a in the liver resulting in glycogenolysis (44). In addition, the conversion of inactive liver glycogen synthetase in the active form was inhibited. Also the activity of phosphoenolpyruvate carboxylkinase, a key enzyme in gluconeogenesis was augmented. Finally, an increase in glucagon release from the islet of Langerhans was observed. These phenomena together led to a rise in blood glucose levels (43). Electrical stimulation of the LHA resulted in reverse changes, i.e., glycogenesis, inhibition of gluconeogenesis and insulin release (43).

Electrical stimulation of the VMH elicited lipolysis in the anesthetized rat (52). However, lipolysis did not occur if stimulation was applied in conscious rats. This discrepancy might be explained, as the authors do in fact, that VMH stimulation causes arousal in conscious rats, which in its turn leads to increased catecholamine output and hence increased lactate formation. Lactate inhibits FFA release probably because of increased reesterification.

Though electrical stimulation may provide some cues regarding possible physiological activities of the stimulated brain areas the method is rather limited with respect to the function during normal ongoing behavior. A much better approach is local application of neurotransmitters and/or neuropeptides for which receptors are present in the area under investigation. This method has also its limitations: the injected or infused substance may spread to adjacent and even more distant areas, or the receptor sites might be reached with difficulty because the synaptic cleft is rather secluded by glia cells.

At present the existence of a number of neurotransmitters and neuropeptides has been demonstrated in each hypothalamic nucleus that is involved in the regulation of food intake and metabolism (36). Monoaminergic neurotransmitters and neuropeptides such as catecholamines like opioid, galanin, etc., may be of primary importance (27). Ingestion of food leads to a simultaneous increased norepinephrine turnover in several parts of the hypothalamus (33,57). Norepinephrine (NE) injection or infusion into the PVN and VMH immediately elicit food intake (24,46). Leibowitz reported that the increase of food intake after NE injection into the PVN was mediated by an α_2 adrenoceptor mechanism (27). The increase of food intake after noradrenergic stimulation of the

PVN was the result of an increase in carbohydrate intake whereas intake of fats and proteins was hardly affected (27). Norepinephrine and especially epinephrine (E) injection into the LHA resulted in a slight suppression of food intake (8,25). Mainly protein ingestion diminished, a phenomenon mediated by a β -adrenoceptor mechanism (8,25). At present many data are available showing that also dopaminergic and serotonergic mechanisms in the hypothalamus are involved in the regulation of food intake. These mechanisms are important especially with respect to the selection of carbohydrates, proteins and fats. Hypothalamic dopaminergic mechanisms seem also to be involved in some aspects of metabolism. Destruction of fibers of passage of dopaminergic nigrostriatal projections in the LHA eliminates elicitation of food intake which normally occurs after peripheral injection of either insulin or 2-deoxyglucose (16). These effects seem to be independent of the aphagia caused by destruction of the LHA since small knife cuts in the nigrostriatal projections laterally of the LHA do not affect the normal food intake and body weight but only abolish elicitation of food intake after either insulin or 2-deoxyglucose injection (16). However, it is unknown whether these cuts interfere with increases and decreases of the plasma substrates glucose and FFA occurring after injection of 2-deoxyglucose and insulin respectively. They lead to severe dopamine depletions in striatum and forebrain. To present more detailed information about the role of brain dopamine, serotonin and neuropeptides is beyond the scope of this short review [for an overview see (16, 27, 34, 35)].

Injection of NE into the hypothalamus does not only elicit food ingestion but also affects blood components related to metabolism. NE injection and infusion into the VMH and PVN causes an increase in blood glucose levels (12, 43, 49). The increase in blood glucose is the result of direct activation of glycogenolysis in liver since injection of NE into the VMH induces an immediate conversion of inactive liver glycogen phosphorylase to active liver phosphorylase (27,43).

Glucagon induced liver glycogenolysis might also contribute because it is reported that noradrenergic stimulation of the VMH caused glucagon release in rats (13) and rabbits (45). Infusion of NE into the VMH resulted in an increase in plasma FFA and insulin (see Fig. 5). The rise of plasma FFA could be observed in spite of a simultaneous increase of blood glucose and plasma insulin. The most plausible explanation is that the VMH can stimulate lipolysis and consequently increase plasma FFA independently of the levels of glucose and insulin. Infusion of NE into the LHA led to an increase in plasma insulin, a decrease in plasma FFA whereas blood glucose and plasma glucagon levels did not change (50). The increase in insulin is parasympathetically mediated because antropepinization of the animals before infusion of NE into the LHA completely eliminated the rise of insulin [(50), see Fig. 6]. Attention has to be paid to the involvement of central adrenoceptors in the regulation of blood glucose, plasma FFA and insulin levels. An abundance of α - and β -adrenoceptors exists in many parts of the hypothalamus (29). Most areas of the hypothalamus receive noradrenergic nerve terminals. In this respect the VMH is exceptional because of a nearly complete lack of noradrenergic innervation (Fig. 1). However, a rich noradrenergic innervation occurs in a shell around the VMH. Therefore it cannot be excluded that adrenoceptors in the VMH are stimulated by NE leaking from nerve endings in this shell and maybe by E.

Shimazu (43) argued that conversion of inactive liver

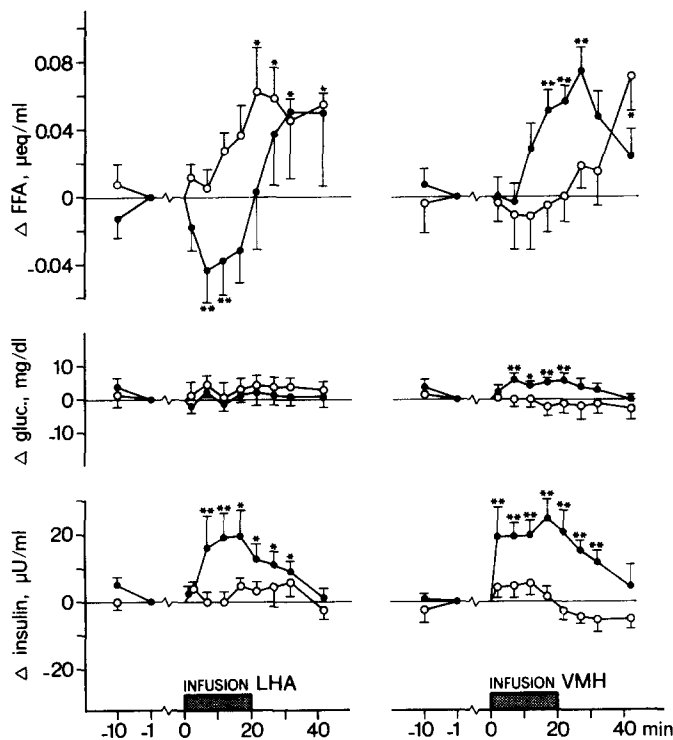


FIG. 5. Effects of norepinephrine (NE) infusion ($25 \text{ ng} \cdot \text{min}^{-1}$ per cannula at a rate of $0.25 \text{ } \mu\text{l} \cdot \text{min}^{-1}$ during 20 min) (●) and diluted solvent infusion (at a rate of $0.25 \text{ } \mu\text{l} \cdot \text{min}^{-1}$) (○) in lateral hypothalamus (LHA) (left panel) and in ventromedial hypothalamus (VMH) (right panel) on plasma FFA, blood glucose and plasma insulin. Data are means \pm SE; μ eq/ml plasma, mg/dl blood, and μ U/ml plasma, respectively changes from preinfusion levels of FFA, glucose and insulin which were average of those of min 1 before infusion start. * Denotes a significant change from preinfusion level. ** Denotes a significant change from diluted solvent infusion (49).

glycogen phosphorylase into the active form after noradrenergic VMH stimulation might be attributed to a β -adrenoceptor mechanism. This conclusion was based on the observation that this effect was blocked by intrahypothalamic application of β - but not α -adrenoceptor antagonists prior to NE injection. Next to it, Barbosa and Migliorini (2) suggested that FFA release is also controlled by a β -adrenoceptor mechanism in the CNS. However, these data were obtained in animals either under anesthesia or in resting conditions. Because an increase of glucose and FFA availability is essential during physical activity we have performed experiments in order to investigate central adrenoceptor mechanisms controlling blood glucose, plasma FFA and insulin levels during swimming in rats. In our experiments rats had to swim for 15 min in a pool filled with water of 33°C against a counter current of 0.22 m/sec . This physical activity resulted in an increase of both blood glucose and plasma FFA whereas plasma insulin declined (Scheurink to be published). These increases mean that production and release of glucose and FFA exceed utilization of these energy substrates. Infusion of the α -adrenoceptor antagonist phentolamine into the VMH just before the start of swimming completely suppressed the rise of glucose during and after swimming whereas FFA levels increased considerably as compared to the control situation. Phentolamine infusion into both the LHA and PVN also caused a complete

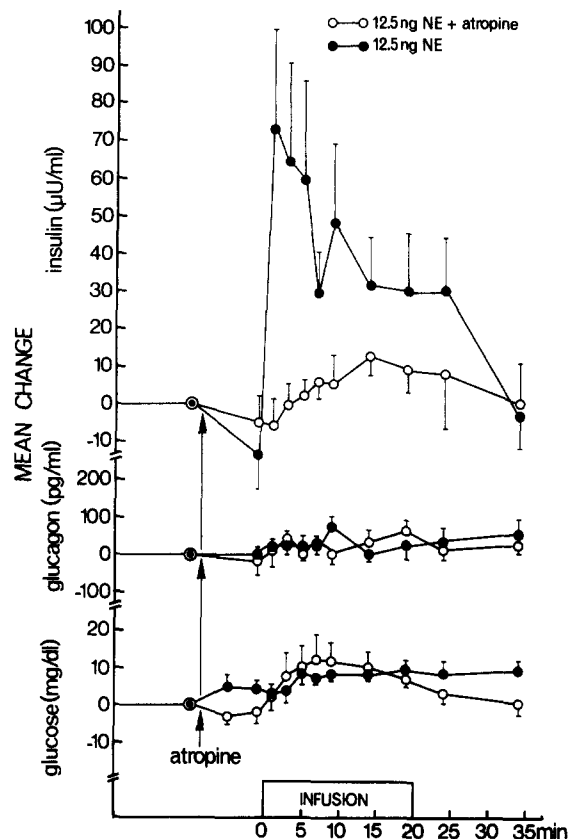


FIG. 6. Effect of NE infusion into the LHA ($12.5 \text{ ng} \cdot \text{min}^{-1}$ per cannula at a rate of $0.25 \text{ } \mu\text{l} \cdot \text{min}^{-1}$ during 20 min) on blood glucose, plasma insulin and glucagon either with atropinization (0.5 mg/kg), ○, or without atropinization, ●. Data are expressed as means \pm SE mg/dl, μ U/ml, pg/ml respectively, changes from preatropinization levels of glucose, insulin and glucagon which were the average of these of time point 1 min before atropinization (50).

suppression of the glucose rise but FFA levels were not affected. Infusion of the β -adrenoceptor antagonist timolol into either VMH or LHA or PVN just prior to swimming caused a transient inhibition of the exercise-induced increase in blood glucose. FFA levels were more or less suppressed during and after swimming with the most pronounced suppression of FFA after β -adrenoceptor blockade of the LHA. This suppression already occurred in the period before the start of swimming when timolol infusion was administered. Regarding the regulation of blood glucose it can be argued that control mechanisms are not restricted to a single hypothalamic nucleus. In addition to a β -adrenoceptor mechanism, as suggested by Shimazu an α -adrenoceptor mechanism operates as well. It is likely that the α -adrenoceptor mechanism is only activated during physical activity. The decreased glucose level during swimming after hypothalamic β -blockade might be due to increased glucose utilization as a response to diminished FFA availability. This suggestion is tenable because decreased FFA utilization due to decreased release leads to diminished citrate and acetyl-CoA induced inhibition of glycolysis so that glucose utilization is enhanced (14,19). In favor of this idea is the strong rebound of glucose immediately after termination of swimming.

Some apparent contradiction in the results needs further

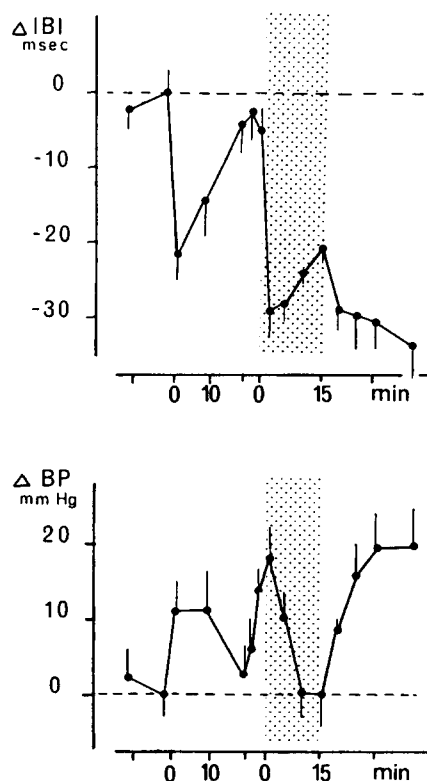


FIG. 7. Changes in heart rate and systolic blood pressure of rats in relation to transfer to the platform of a swimming pool (first 0 min), during swimming against a counter current (0 to 15 min, shaded area) and the postswimming period on the goal-platform. Changes mean heart rate changes $\pm S.E.M.$ are calculated from the measurement of interbeat intervals (IBI) in msec. A decrease of IBI indicates a tachycardia. Mean systolic blood pressure (BP) $\pm S.E.M.$ is expressed in mmHg.

elucidation. We found that both noradrenergic stimulation of the VMH in resting animals and α -adrenergic blockade of the VMH in exercising animals resulted in increased plasma FFA levels. Thus both adrenergic stimulation and inhibition of the VMH resulted in an increase of plasma FFA. It is conceivable that stimulation of an α -adrenergic network in the VMH is responsible for glucose release and stimulation of a β -adrenergic network for FFA release. The α - and β -adrenoceptors in these networks are postsynaptic. Besides these postsynaptic adrenoceptors also presynaptic α -adrenoceptors have been postulated. Activation of the presynaptic α -adrenoceptors leads to a diminished NE release from the presynaptic nerve terminals. Conversely, blockade of these receptors resulted in increased NE release. In experiments in which NE is administered into the VMH it may result, because of the large amount of NE available, in stimulation of the postsynaptic α - and β -adrenoceptors leading to glucose and FFA release. Infusion of phentolamine leads to a blockade of the presynaptic α -adrenoceptors and therefore to enhanced release of NE from the presynaptic nerve endings. As a consequence, an increased β -adrenoceptor stimulation occurs postsynaptically evoking increased FFA release. Because of the presence of phentolamine the postsynaptic α -adrenoceptors are blocked so that in spite of increased release of NE from

presynaptic neurons the α -adrenoceptor dependent neural network involved in glucose release is not stimulated. At present little is known about the precise typology of the VMH adrenoceptors regulating glucose and FFA release. Further investigations are necessary to subdivide the receptors in α_1 , α_2 , β_1 and β_2 types. It should be noticed that a comparable, if not the same central receptor systems as involved in both glucose and FFA regulation might control food intake.

It is evident from the above mentioned data that the hypothalamus exerts powerful effects on blood glucose and plasma FFA especially during physical activity. Now the question arises as to which pathways between the hypothalamus and the target organs, i.e., the liver and the adipose tissue may be involved. With respect to glucose the following mechanisms may be involved: 1) direct sympathetic innervation of the liver, 2) E release from the adrenal medulla, 3) glucagon release from the A cell of the islet of Langerhans. With respect to FFA both the sympathetic system and the pituitary may play a role. These assumptions are, at least partly, confirmed by the above mentioned exercise experiments, where swimming caused an increase in both E and NE levels. This can explain the increase of glucose and FFA. However, as appears from the work of Bray, pituitary influences cannot be excluded (10). Furthermore, it should be noticed that E in physiological quantities only affects glucose production and not FFA release, whereas NE released by the sympathetic nerve ending stimulates both glucose as well as FFA release (Scheurink, to be published).

Alterations in catecholamine concentrations may also contribute to cardiovascular reactions. Therefore, we measured blood pressure (BP) in rats in a direct way through a preimplanted catheter in the ascending aorta. Heart rate (HR) was derived either from the systolic blood pressure waves by measuring the interval elapsed between the systolic peak pressures (Interbeat Intervals, IBI). The changes in mean IBI (expressed in msec) and BP (measured in mmHg) that occur in conjunction with handling, exposing to the swimming pool, swimming and the postswimming period are depicted in Fig. 7. Transfer of rats to the starting platform resulted in a substantial increase in heart rate (as indicated by a shortening of IBIs) and a moderate increase in mean BP in comparison to resting baseline levels. Twenty min later both the mean IBI and BP returned practically to baseline levels. Lowering the starting platform to the water surface led to an increase in BP, but no changes in IBI occurred. However, a very rapid increase in heart rate occurred in the first min of swimming with a further moderate rise of BP. Both the IBI and BP values at the onset of swimming represented the peak changes that occurred. Measures taken 5 and 10 min after the onset and immediately before termination of swimming showed a steady decrease of both heart rate and BP. The BP of the rats did return to baseline at 10 min. The heart rate, however, remained higher than the baseline during the entire swimming period. The postswimming period on a heated goal-platform was characterized by a substantial increase of both heart rate and BP. Both changes slightly exceeded the peak values obtained during swimming. Vigorous grooming and wet-shaking characterized this period. The results suggest that there seems to be a coupling between BP and the rise of E, whereas the HR change seems to occur independently of BP and plasma catecholamine alterations. For example, a most conspicuous observation is the combined rise of E and blood pressure when the paws of the rats were getting wet, i.e., already before the start of the

swimming performance whereas NE rose only during swimming (Scheurink, to be published). This means that E and BP already rose in the period when activity was expected. Since plasma NE levels did not change in this period it is likely that the primary increase in BP that reflects expectation of activity is mediated by E release from the adrenal medulla. Such predictive changes in the heart rate and substrate release were absent. Since expectation often occurs in form of increased vagal activation (9), it is possible that due to a low baseline heart rate a further bradycardia cannot be manifested.

The cardiovascular requirements for swimming seem to be secured by a high heart rate with practically unchanged blood pressure. The decline of BP appeared to be parallel with a decline in circulating E concentration. This finding further reinforces the notion of an adrenal medullary control of BP in relation to swimming as exercise. The tachycardiac heart rate showed no relation to plasma NE levels. While the IBI showed a slight increase—i.e., moderate decrease in tachycardia—the plasma NE levels increased steadily (Scheurink *et al.*, submitted). It remains, therefore, to be shown whether this decrease was caused by increasing vagal influence.

The postswimming period with a secondary increase in both heart rate and BP as well as of circulating catecholamines (Scheurink *et al.*, to be published) requires further attention. Besides vigorous muscular activities, thermoregulatory processes may also contribute to the activation of the cardiovascular system.

Various hypothalamic nuclei serve the control of the car-

diovascular system (47). Unfortunately, little is known about the hypothalamic control of the cardiovascular system during physical exercise. Since BP changes seem to be related to the release of E from the adrenal medulla, the available neuroanatomical and physiological data suggest that those hypothalamic nuclei participate in the control processes that regulate the hormone output through the sympathetic nervous system. It is difficult to presuppose the localization of the control of heart rate response during exercise of swimming. One of the possible mechanisms is a regulatory influence on the vagus nerve. As shown earlier in this paper, hypothalamic nuclei have direct or indirect connections with the dorsal motor nuclei of the vagus nerve.

CONCLUDING REMARKS

Physiological experiments suggest that various components of metabolic and cardiovascular responses in relation to energy expenditure are differentially organized at the hypothalamic level. Further neuroanatomical and complex physiological-neuroendocrinological experiments are necessary to elucidate whether the control mechanisms of the adrenal medullary, cardiovascular and metabolic processes by the autonomic nervous system are using the very same neurons from the hypothalamus on, or if different neurons in the same branch convey the hormonal, cardiovascular and metabolic messages to the periphery. That differential response can be obtained within the various branches of the sympathetic nervous systems upon hypothalamic stimulation (22) supports the latter view.

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